Remarks

Applicants appreciate the Examiner's thorough examination of the application. Applicants respectfully requests reconsideration of the claims under examination based on the foregoing amendments to the claims and the following remarks.

Claims 1-3, 5-32 are pending in the application. Claims 1, 5-8, 10-11, 13, 16, 18-19, 21, 23-26 and 31 are amended. No new matter has been introduced by the instant amendments to the claims. Applicants reserve the right to pursue the subject matter cancelled by this or a prior action in this or a subsequent continuation application.

Claims 1,5-7 stand rejected under 35 U.S.C.§102(b) as being anticipated by Verma et al. (CA 111:224813).

Claims 1-3, 5-12, 14-32 stand rejected under 35 U.S.C.§103(a) as being unpatentable over Jacobsen patents taken with Verma.

Claims 14-32 stand rejected under 35 U.S.C.§112, first paragraph, due to lack of enablement.

Claims 5-8, 10, 13, 18, 21 and 25 are rejected under 35 U.S.C.§112, second paragraph as indefinite.

Rejection under 35 U.S.C.§102(b)

Claims 1,5-7 are rejected under 35 U.S.C. § 102(b) as being anticipated by Verma et al (CA 111:224813). The rejection is respectfully traversed.

The Verma reference disclosed compounds (compounds are Racemic) having more than one stereogenic center, resulting in not just two enantiomers, but in 2^{n-1} pairs of enatiomers (where n is the number of stereogenic centers). Unlike in case of enantiomers with one chiral center, the genus contains exactly two species, which is a very small genus, chiral molecules with several stereogenic centers, mere disclosure of the potentially large numbers of candidate molecules does not anticipate the one that is pharmacologically most beneficial.

As stated above, the Verma reference disclosed racemic compounds having three asymmetric centers (three stereo/chiral centers). Thus, it is possibly a mixture of eight enantiomers. The reference defines the stereochemistry of the C3 stereogenic center and does **not** define the stereochemistry of the C4 carbon or the stereochemistry of stereogenic centers, if any, present on the substituent of the C4 aromatic ring. In other words, there are still two other stereo center present in nucleus (chromane) which are unresolved chiral center. Thus, compounds disclosed in the Verma reference still may be mixture of four isomers.

Further, the Verma reference neither disclosed not taught which isomer will be active for the intended use of the present invention. Further, the Verma reference neither disclosed nor taught the activities such as antiosteoporosis (antiresorptive), antiproliferative anticancer and hyperlipidaemic properties disclosed in the present application.

In contrast, the instant invention provides compounds of Formula I in which the stereochemistry of the C3 carbon (bearing the R_2 residue), the C4 carbon (bearing the R_3 residue) and the stereogenic center of the OR_5 residue are specified and thus single enantiomer. More particularly, the compounds provided by claim 1 include those in which R_2 and R_3 are in a *trans* relationship and OR_5 comprises either a *R* or *S* configuration at the side chain (but not a racemic mixture thereof).

The basic concept of the present invention is to show the effect of stereocenter in antiestrogen side chain. Although Tamoxifen, Raloxifene, centchroman all have similar chains, none of these compounds have stereocenter in antiestrogenic side chain. It is the inventors of the present invention that first introduced a stereocenter in antiestrogenic side chain in form of substituted amino-2-hydroxy propyloxy phenyl, and that resulted in a first discovery that stereo center at antiestrogenic side chain have increased antiresorptive, antiproliferative activity. Beside this only one particular stereoisomer in side chain have shown less toxicity (uterotrophic activity).

For at least the preceding reasons, the Verma reference does not anticipate claim 1. Moreover, Verma fails to teach or suggest that specifying the stereochemistry and diastereochemistry of the recited compounds would be desirable. Thus, claim 1 is also non-obvious over the Verma reference.

Rejection under 35 U.S.C. § 103(a)

Claims 1-3, 5-12 and 14-32 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Jacobsen patents (USP 5,985,306 or USP 5,994,390 or USP 6,316,494 B1 or USP 6,043,269) taken with Verma.

The office action dated 4/5/2006 stated that "Jacobsen references generically disclosed 3,4-diarylchroman compounds" and "sole difference is the R3 position being phenyl-O-(CH2)n-Y wherein n is 1-12" and the claimed compounds have R3 position being phenyl-O-CH2-CH(OH)-CH2-Y". The Office Action recognized that the *reference do not teach the equivalence of H and OH on the carbon.* The Office Action further stated that the Verma reference taught species where R3 position is phenyl-O-CH2-CH(OH)-CH2-Y. Thus, according to the Office Action, one of ordinary skill in the art would be motivated to modify Jecobsen compound genus to replace H with OH according to Verma reference. In addition, the Office Action stated that skilled artisan would be motivated to modify Jacobsen as the compounds are structurally similar to those of Verma with the expectation of retaining the estrogen activity as the compounds are structurally similar with same properties.

The rejections is respectfully traversed. In the recently decided case, *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, Fed. Cir., No. 06-1329, 6/28/07, the court stated:

> "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner

> to establish prima facie obviousness of a new claimed compound,"

Here, the Jacobsen's '306, '494, and '269 patents merely recite *cis*-chromane compounds having a variety of side chains which are structurally divergent from the OR_5 residues of the instantly claimed invention.

The '390 patent neither teaches nor suggests compounds in which the substituent on the 4-phenyl ring comprises a stereogenic center. In addition, the '390 patent neither teaches nor suggests compounds in which the substituent on C2 position of chromane ring. Moreover, the '390 patent fails to teach or suggest compounds having an OR_5 residue on the 4-phenyl substituent of the chromane ring, which R_5 group has a single enantiomer stereogenic center. Thus, none of Jacobsen taught or suggested the compound of the present invention.

Further, as stated above, the Verma reference neither teaches nor suggests compounds of Formula I in which the stereochemistry of the C3 carbon (bearing the R_2 residue), the C4 carbon (bearing the R_3 residue) and the stereogenic center of the OR_5 residue. The Verma reference merely disclose mixture of 8 or 4 isomers. The Verma reference neither teaches nor suggests the single enantiomer with well defined stereochemistry of the compound of the present application.

In contrast, the compounds of claim 1have the stereochemistry and diastereochemistry of the stereogenic centers specified. The compounds of the present invention have asymmetric center. Further, the compounds of claim 1 have gem alkyl substitution at C2 position of chromane ring. In addition, the structure of the OR_5 side chain of the compounds of the instant invention are completely different from those recited in any of the four Jacobsen patents. For example, the compounds of claim 1 have substituted amino 2-hydroxy propyloxy phenyl at para position of C-4 phenyl ling, which is totally different from the side chain attached at the same position of the compounds disclosed in the Jacobsen references, which is pyrrolidinoethoxy phenyl. Moreover, the compounds of the present invention have different side chain with one stereo center.

Thus, the Verma reference neither suggested nor taught the reason that would have led a chemist to modify Jacobsen compound in a particular manner to establish prima facie obviousness of a new claimed compound in the present application.

The compounds of the present invention is designed to show the effect of stereo center in anti-estrogenic side chain. Applicants introduced a streo center in side chain in form of substituted amino 2-hydroxy propyloxy phenyl and that resulted in the unexpected discovery that stereo center at antiestrogenic side chain have enhanced biological activity with less toxicity (uterotrophic activity). Neither the Jacobsen reference nor the Verma reference suggested or taught the single enatiomer with well defined stereochemistry of the present invention. Moreover, neither references suggested or taught that the single enantiomer shows unexpected enhanced activity with low toxicity.

For at least the above reasons, claim 1 is patentable over each of the four Jacobsen patents or any combination thereof. Claims 2-12 depend from claim 1, claims 14-32 use the compound of claim 1, and are therefore also patentable over the disclosure of any of the four Jacobsen patents taken with the Verma reference.

Claims 1, 5-7 stand rejected under 35 U.S.C 103(a) as being unpatentable over Verma that teach species according to the invention.

The rejection is respectfully traversed. The Verma reference merely disclosed comparison of activity of 3,4-diaryl chromenes and trans-3,4-diaryl chromans. The Verma reference has nothing to do with the effect of stereocenter in antiestrogen side chain. Further, the Verma reference only studied a possible link between the anti-inflammatory property and antifertility activity based on mere speculation.

Thus, the Verma reference neither suggest nor taught any expectation of successfully obtain the claimed compound with intended effect based on the difference of stereochemistry.

Rejection under 35 USC §112, first paragraph

Claims 14-32 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for treating estrogen dependent diseases/disorders, does not reasonably provide enablement for preventing estrogen dependent diseases/disorders. The Office Action dated 4/5/2006 stated as follows:

> How is it determined 'who' needs prevention? That the disease will not ever occur initially, which is what 'prevention' is, has not been established. Preventing is seen as an all or nothing phenomenon, and applicant must prove the negative. There is insufficient support for preventing the named diseases and the skilled artisan would not know that the treatment would prevent all the named diseases.

The applicants respectfully disagree. As stated in the previous response, the state of the prior art indicates that prevention of estrogen related disease/condition is possible. For example, in Dwivedy et al., 1995 "Recent Developments in the Chemotherapy of Osteoporosis", Progress in Drug Research 45, 289-338, which is cited on page 3 of the specification and submitted as CA in IDS, on page 325, hormone replacement treatment (HRT) is mentioned as preventive measure for risk patients and preclinical osteoprosis. It mentioned detection of onset of osteoprosis before it leads to a fracture and the extent of the disease even after the damage, by bone density measurements and evaluation using biochemical markers. Id at 323. By using these methods, practitioners can identify risk patients who have not developed osteoporosis but have a higher probability of developing the disease, or preclinical osteoporosis which is a stage when some reduction in bone mass has occurred. Use of HRT is suggested for preventive purpose. Id at 325. Similarly, in Marshall et al., 1977 "The Prevention and Management of Post-Menopausal Osteoporosis" Acta Obstet Gynecol Scand (Suppl) 65:49-56, which is cited on page 3 of the specification and submitted as CB in IDS, on page 52, "[I]n view of the data quoted above, it is hardly surprising that oestrogen therapy prevents or delays post-menopausal bone loss." It suggested "that at the present state of knowledge some indication of the rate of bone loss can be derived from the fasting urinary hydroxyproline and that patients with consistently raised values are probably the ones who require oestrogen preventive therapy from the bone point of view." Id. at 53. In addition, Stampfer et al., 1991, "Estrogen Replacement Therapy and Coronary Heart Disease: a Quantitative Assessment of the

Epidemiological Evidence" Preventive Medicine 20:47-63, which is cited on page 3 of the specification and submitted as CF in IDS, concluded on page 61 "[T]he preponderance of evidence from the epidemiologic studies strongly supports the view that postmenopausal estrogen therapy can substantially reduce the risk for coronary heart disease."

Thus, skilled artisan who is familiar with estrogen related disease/condition is able to determine which ones could be prevented by administering the claimed compound.

Further, the compounds of the present invention actually have for example, antiosteoprosis (antiresorptive) activity, which is supported on page 52, under "Test procedure for evaluation of antiosteoporosis (antiresorptive) activity in in vitro", with the results in Table 1 on page 53, of the specification.

Accordingly, the amount of guidance necessary to perform applicant's invention would not result in undue experimentation.

As to claim 21, the applicant again would like to take the Examiner's attention to the language of claim 21. Claim 21 is directed to a **method** of prevention and/or treatment. The method helps in preferably diseases or syndromes caused by an estrogen-deficient state, with Relative Binding affinity (RBA) to estrogen receptors ranging between 5 to 7.

Applicant believes the relevant point is not the number of compounds, but compounds with RBA 5 to 7 is therapeutically effective in preventing and/or treating listed disorders. As Phytoestrogens and Mycoestrogens Bind to the Rat Uterine Estrogen Receptor, Branhams et al., J. Nutr. 132:658-664 (2002) (hereinafter Branhams), which is cited by the Office, described, the estrogen receptor (ER)-ligand competitive binding assay is known to quantitatively assess a chemical ability to bind to the ER. The ligand is 17β-estradiol and the reduction in plasma levels of the 17β-estradiol less than 10 % of pre-menoposal values is major characteristics of post-menoposal stage and resulting in a number of chronic disorders(page 2, ll. 18-22 in the specification) Estrogen replacement therapy is beneficial for those chronic disorders, but the dose and duration of estrogen therapy is also associated with an increased risk of endometrial hyperplasia and carcinoma (page 6, l.22 to page 8, l. 32 of the specification).

The applicant would like to further take the Examiner's attention to paragraph 6 of the attached Rule 132 declaration by Dr. Kumar, one of the inventors. Dr. Kumar stated:

> Literature knowledge about (RBA) shows that RBA (1to 7 or more) is more likely to show biological response. Compounds like Tamoxifen have RBA (5)[1,2] and is a drug for anticancer breast. Beside this compounds like Nafoxidine, Toremifene and Clomiphene have RBA ranges from (0.7 to 1.3)[3] but showing very good biological activity. Compound showing RBA (5-7) have quit good affinity towards estrogen receptor and more likely to show biological response.

As sited in the declaration as reference 1, Johnson et al, Idoxifene Antagonizes Estradiol-dependent MCF-7 Breast Cancer Xenograft Growth through Sustained Induction of Apoptosis, CANCER RESEARCH 59, 3646–3651, August 1, 1999, described Tamoxifen, which is known as a drug for anti-breast cancer has RBA of 5 (table 1 in page 3647) (see also, abstract of Jordan et al, Determination and Pharmacology of an New Hydroxylated Metabolite of Tamoxifen Observed in patient Sera during Therapy for Advanced Breast Cancer, CANCER RESEARCH, 43, 1446-1450 ,March 1983, showing RBA 6 for Tamoxifen). Both of the references together with Blair et al., Toxicology Sciences 54,138-153 (2000), The Estrogen Receptor Relative Binding Affinities of 188 Natural and Xenochemicals: Structural Diversity of Ligands (all are cited in the declaration) are attached herewith and submitted as IDS which is also attached to this response.

As stated above, RBA is well known in the art and those having RBA 5-7 have known to have therapeutic effect. In addition, how it is determined is well described in page 60-61 of the specification. Thus one skilled in the art would have known to determine which compounds would be in the BRA range of 5-7 and that compound having RBA range 5-7 has therapeutic effect.

Accordingly, one skilled in the art, based on knowledge of compounds having similar physiological and/or biological activity would be able to discern the embodied invention, thus sufficient to satisfy 35 U.S.C.§112, first paragraph.

Rejection under 35 U.S.C.§112, second paragraph

Claims 5-8, 10, 13, 18, 21, 23-26 and 31 are rejected under 35 U.S.C.§112, second paragraph as being indefinite due to terms "preferably" or "preferred". Applicants deleted "preferably", "preferred" and "in particular" from claims 5-8, 10, 13, 18 and 21 and amended appropriately, if necessary.

Claims 11, 13 and 19 are amended in order to further clarify, the applicant amended the language "such as" to "including".

Claim 8 has been amended to remove internal periods to make the claim proper Markush ending.

Claims 8 and 25 have been amended by adding "or" between the last two ingredients, as suggested by the Office Action.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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